FORM PTO-1390 (REV 11-98) | U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	
Bayer 10197-CAO	
U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	
09/402737	
INTERNATIONAL APPLICATION NO. PCT/EP98/01926	INTERNATIONAL FILING DATE 2.April 1998 (02.04.98)
PRIORITY DATE CLAIMED 15.April 1997 (15.04.97)	

TITLE OF INVENTION: ANALGESIC COMBINATION

APPLICANT(S) FOR DO/EO/US: Dieter NEUSER; Monika FIERUS; Wolfgang WIEHL

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☐ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    a) Appendix
    b) Copies of:
    -WO 98/46235 (World Publication)-in German with English Abstract
    -PCT/ISA/210 (International Search Report) - in English and German
    -PCT/IPEA/409 (International Preliminary Examination Report) - in German
    -PCT/RO/101 (PCT Request) - in German

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/402737	PCT/EP98/01926	Bayer 10197-CAO

17. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	CALCULATIONS PTO USE ONLY
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO $970.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO $840.00	
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO $760.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) $670.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) $96.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 840.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 0

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	4 - 20 =	0	X $18.00	$ 0
Independent claims	1 - 3 =	0	X $78.00	$ 0
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $260.00	$ 0
TOTAL OF ABOVE CALCULATIONS =				$ 840.00
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also by filed (Note 37 CFR 1.9, 1.27, 1.28).				$ 0
SUBTOTAL =				$ 840.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$ 0
TOTAL NATIONAL FEE =				$ 840.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$ 0
TOTAL FEES ENCLOSED =				$ 0
			Amount to be: refunded	$
			charged	$ 840.00

a. ☐ A check in the amount of $_____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. 02-1445 in the amount of $ 840.00 to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-1445. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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REGISTRATION NUMBER

Analgesic combination

The present invention relates to medicinal preparations which can be administered orally and contain a fixed combination of at least one locally acting analgesic with a rapid onset of action and at least one systemically acting analgesic with a sustained action.

Locally acting analgesics with a rapid onset of action which can be used, for example, in the form of sprays or pastilles are already known. Local anaesthetics of this type display their action after less than one minute but have only a short duration of action so that frequent remedication is necessary, which adversely affects safety and patient compliance.

Examples of particularly interesting locally acting analgesics which may be mentioned are the benzocaines. They inhibit impulse formation and conduction in nerves by blocking the flow of sodium.

Systemically acting analgesics, such as, for example, NSAIDs, in particular acetylsalicylic acid (ASA), represent another useful possibility for alleviating pain. These analgesics reduce the sensitivity of the nociceptors, and the alleviation of pain can be explained by the inhibition of prostaglandin synthesis. With most of these systemically acting analgesics, the maximum activity is not reached until after about 1-2 hours.

An object of the present invention is to satisfy the need, which has existed for a long time, to provide a preparation which can be administered orally and which combines, in a simple and reliable manner, an immediate analgesic action with a sustained action.

The active substances which can be used as locally acting analgesics (element A) are those which show a significant onset of action within a period of up to 10 minutes, preferably of 4 minutes, in particular of 1 minute and very particularly of 30 seconds.

The locally acting analgesics (combination element A) are expediently employed in amounts of from 0.5 to 100 mg, preferably 1 to 60 mg and, in particular, 2 to 30 mg, per individual administration form.

The combination according to the invention may contain one or more local anaesthetics as element A, for example 1, 2 or 3. Combinations with only one compound of element A are of particular interest.

The active substances of element A are substantially known. Particularly suitable examples which may be mentioned are ester-type local anaesthetics such as benzocaine, amethocaine, amylocaine, butacaine, butoxycaine, butyl aminobenzoate, chloroprocaine, chlormecaine, cyclomethycaine, isobutamben, meprylcaine, oxybuprocaine, procaine, propipocaine, proxymetacaine, tricaine etc. Mention may likewise be made of anilide-type local anaesthetics such as lidocaine, bupivacaine, butanilicaine, carticaine, cinchocaine, clibucaine, etidocaine, mepivacaine, oxethazaine, prilocaine, ropivacaine, ethyl p-piperidinoacetyl-aminobenzoate, tolycaine, trimecaine, vadocaine, etc.

It is also possible to employ other local anaesthetics such as, for example, pramoxine or essential oils such as menthol or eucalyptus oil.

The systemically acting analgesics which can be employed as element B are likewise substantially known. Mention may preferably be made of non-steroidal antiinflammatory drugs (NSAIDs) such as, for example, phenylacetic acid derivatives such as aceclofenac, alclofenac, bromofenac, diclofenac, fenclofenac etc., arylacetic acid derivatives such as acemetacin, amfenac sodium, bendazac, glucametacin, oxametacin, etc., para-aminophenol derivatives such as acetanilide, etc., propionic acid derivatives such as alminoprofen, ibuprofen, ketoprofen, flurbiprofen, naproxen, oxaprozin, salicylic acid derivatives such as acetylsalicylic acid (ASA), aluminium ASA and other salts, diflunisal, etersalate, fosfosal, salol, salsalate, salacetamide, etc., pyrazolone derivatives such as amidopyrine, dipyrone etc., oxycam derivatives such as droxicam, isoxicam, piroxicam etc., phenylbutazone derivatives such as azapropazone, bumadizone calcium, oxyphenbutazone etc., pyranoindoleacetic acid derivatives such as etodolac etc., anthranilic acid derivatives such as glafenine, Na meclofenamate, mefenamic acid, morniflumate etc., indole derivatives such as indomethacin etc., paracetamol and paracetamol derivatives and other NSAIDs such as anirolac, benzpiperylone, benzydamine hydrochloride, Na butibufen, chlorthenoxazine, cinmetacin, clonixin, cloracetadol, difenpiramide, diproqualone, etenzamide, famprofazone, flupirtine maleate, ibuproxam, indoprofen, isamfazone, meloxicam, metiazinic acid, metifenazone, nifenazone, niflumic acid, mimesulide, pirazolac, pranoprofen, proquazone, protizinic acid, ramifenazone etc.

The systemically acting analgesics of element B are employed according to the invention in amounts of from 5 to 1500 mg, preferably 8 to 1000 mg, in particular 10 to 800 mg, per dosage form.

The local analgesics preferably employed as element A are rapidly acting and have an optimal duration of action lasting 0.5 to 120 minutes, preferably 2 to 60 minutes, in particular 5 to 30 minutes. The systemic analgesics preferably used as element B are those where a significant action has its onset after 15 minutes and lasts for up to 24 hours, preferably those whose action has its onset after 20 minutes and lasts for up to 12 hours, in particular up to 8 hours.

Particularly interesting combinations according to the invention are those which contain as element A an ester-type local anaesthetic, in particular benzocaine, and contain as element B propionic acid derivatives or salicylic acid derivatives, in particular ASA.

Preferred systemic analgesics are those which have a duration of action of at least 3 hours.

The combination according to the invention is particularly suitable for treating inflammatory and/or painful disorders of the oropharynx, in particular for treating pharyngitis, laryngitis, tonsillitis, stomatitis, gingivitis of a variety of aetiologies. The combination product according to the invention is expediently administered orally.

The combination can be employed in conventional formulations, the intention being that the local anaesthetic is released first, and it being possible for the systemically acting analgesic where appropriate also to be present in depot form. The following may be mentioned as examples of such preparations: press-coated tablets, coated pastilles, chewing gum, hard caramel with liquid, semisolid or solid core. They are produced by conventional methods using customary ancillary substances.

Examples

Example 1

A tablet of the following composition may be mentioned by way of example:

ASA core tablet:

500 mg of ASA are compressed with 30 mg of ascorbic acid, 75 mg of sucrose, 47 mg of microcrystalline cellulose, 2 mg of saccharin (550 ×) and 6 ml of orange juice flavouring to give a tablet with a total weight of 660 mg. These core tablets are coated uniformly with a benzocaine-containing coating syrup, applying a total of about 5 mg of benzocaine and 602 mg of coating syrup. The aforementioned tablet shows a marked analgesic action only two minutes after intake, and this is sustained for a period of more than 3 hours.

Example 2

A core tablet containing 300 mg of naproxen is coated with a coating syrup which contains 500 mg of lidocaine in analogy to Example 1. This combination preparation shows an onset of action after 2 minutes and a duration of action of more than 6 hours.

Patent Claims

1. Preparation which can be administered orally and contains a fixed combination of at least one locally acting analgesic with a rapid onset of action (element A) with at least one systemically acting analgesic with a sustained action (element B).

2. Preparation according to Claim 1, characterized in that the active substance employed as element A shows an optimal duration of action of from 0.5 to 120 minutes, and the active substance employed as element B has an action of from 15 minutes up to 24 hours.

3. Preparation according to Claim 1, characterized in that elements A and B are selected so that the fixed combination has a duration of action of from 2 minutes up to 12 hours.

4. Process for producing a preparation according to Claim 1, characterized in that the fixed combination of an active substance of element A and an active substance of element B are converted together with conventional ancillary substances and carriers and, where appropriate, other compatible active substances into a suitable administration form.

Analgesic combination

Abstract

The present invention relates to medicinal preparations which can be administered orally and contain a fixed combination of at least one locally acting analgesic with a rapid onset of action and at least one systemically acting analgesic with a sustained action.

COMBINED DECLARATION AND POWER OF ATTORNEY	ATTORNEY DOCKET NO

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name. I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought
on the invention entitled

"ANALGESIC COMBINATION"

the specification of which is attached hereto,

or was filed on **April 2, 1998**

as a PCT Application Serial No. **PCT/EP98/01926**

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s), the priority(ies) of which is/are to be claimed:

197 15 594.4	**Germany**	**April 15, 1997**
(Number)	(Country)	(Month/Day/Year Filed)

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose the material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occured between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith:

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